REMARKS

Prior to the present amendment, claims 1-20 were pending. The examiner has withdrawn claims 4-12 for being directed to a non-elected invention. By this amendment, claims 1, 14 and 15 have been amended. Accordingly, claims 1-3 and 13-20 are under consideration. Reconsideration is respectfully requested.

Withdrawal of Objection and Rejections

On page 2 of the office action, the examiner withdrew the objection of claim 21, and the rejections of various claims under 35 U.S.C. 112 first paragraph and second paragraph. Applicants appreciate the examiner's consideration and the progress made with the case.

Rejection under 35 U.S.C. 103(a) over Schmitt, Alpar, and Isaka

On pages 2-3 of the office action, claims 1-3 and 13-21 were rejected under 35 U.S.C. 103(a) allegedly for being obvious over Schmitt et al., (*J. Pediatrics,* 2000, 137:304-312), Alpar et al., (*Adv. Drug Delivery,* 2001, 51:173-201), and Isaka et al., *(Vaccine,* 2001, 19:1460-1466).

The examiner has applied this rejection to claims 1-3 and 13-21. Applicants note that claim 21 was cancelled in the amendment dated September 7, 2006. Therefore, applicants are addressing this rejection as being applied to claims 1-3 and 13-20.

The examiner states that Schmitt et al. teaches a multivalent vaccine formulation containing hepatitis B virus surface antigen (HBsAg), diphtheria, tetanus, *Haemophilus influenzae type b,* and inactivated poliovirus given as either separate or mixed injections.

The examiner acknowledges that Schmitt et al. does not teach the vaccine for intranasal administration. To rectify the deficiency, the examiner cites Alpar et al. and Isaka et al.

According to the examiner, Alpar et al. teaches intranasal formulations for tetanus toxoid and diphtheria. The examiner states that Isaka et al. teaches intranasal administration of HBsAg alone or with rCTB as adjuvant in a mouse model. Therefore, the examiner concludes that it would be obvious to administer the formulation of Schmitt et al. intranasally because Alpar et al. and Isaka et al. teach nasal administration of HBsAg or tetanus toxoid and diphtheria. Applicants respectfully disagree.

In the September 7, 2006 amendment, applicants argued that there is no disclosure or suggestion that the HBsAg in the formulation of the cited references is an immunoenhancer of other antigens, as is required in the claimed invention. Applicants further directed the examiner's attention to Tables I and III of Schmitt et al. There, Schmitt et al. discloses that the other antigens, such as diphtheria and tetanus, are either comparable or less immunogenic when administered in a mixture with HBsAg, than when administered separately. In response, the examiner states that the immunogenicity of HBsAg and its effect on other antigens, such as immunoenhancement, is an inherent property of HBsAg.

Applicants respectfully disagree with the examiner's contention that the ability of HBsAg to immunoenhance other antigens is an inherent property of HBsAg. In order to establish the theory of inherency, "the Examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied art." Ex parte levy, 17 USPQ 2d, 1461, 1464, (Bd. Pat. App. & Inter. 1990) (Emphasis in Original). See MPEP §2112. In the instant application, the examiner has not provided the necessary evidence that all HBsAg have an immunoenhancing effect.

Not all HBsAg have an immunoenhancing effect. Thus, the theory of inherency is not applicable.

The immunogenicity of HBsAg differs depending on the host system utilized to produce the antigen. Host systems differ in their chemical modifications of a protein after its synthesis. Such chemical modifications (e.g., post translational modifications), such as the attachment of various lipids and carbohydrates, contribute to an antigens immunogenicity, and its ability to immunoenhance other antigens in a formulations.

Merely in order to expedite prosecution, applicants have amended the claims to include the limitation that the HBsAg is a recombination antigen produced by the host system *Pichia pastoris*. Nowhere in the cited references is there any disclosure or suggestion that the HBsAg is produced by *Pichia pastoris*. Nor is there any disclosure or suggestion of nasal administration of HBsAg from *Pichia pastoris*. Without such disclosures in the cited references, the claims as amended cannot be said to be obvious over Schmitt et al., Alpar et al. and Isaka et al.

Support for the limitation that the HBsAg is produced by *Pichia pastoris* is found in the specification as originally filed, see page 20, line 27. There, it is disclosed that the HBsAg used is Heberbiovac HB®.

Heberbiovac HB® is a commercially available HBsAg produced by *Pichia pastoris*. Applicants submit herewith two articles evidencing that Heberbiovac HB® is a trademark for HBsAg produced by *Pichia pastoris*. See, for instance, the introduction in the article by Hardy et al., (*Biotecnologia Aplicada*, 2000, 17:52-53) and the last paragraph in the introduction and the paragraph bridging pages 498 and 499 of the article by Sethi et al., (*Indian Pediatrics*, 1999, 36:498-501).

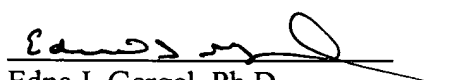
European Patent Application No. EP0864649A2, a copy of which is enclosed for the examiner's convenience, discloses in example 6 an experiment which demonstrated that HBsAg produced by *Pichia pastoris* is more immunogenic than the commercially available HBsAg from Smith Kline and produced by *Saccharomyces cerevisiae*.

The specification of the instant application demonstrates the unexpected and surprising results obtained with the multivalent vaccine formulation of the invention. The examples and figures show the ability of nasally administered HBsAg from *Pichia pastoris* to enhance the immunogenicity of various antigens. For example, figure 1B shows that the immunogenicity of tetanus toxoid is enhanced when nasally administered with HBsAg (group 3) than when tetanus toxoid is administered alone (group 11). In addition, figure 1C shows that the immunogenicity of diphtheria toxoid (group 1) is enhanced when nasally administered with HBsAg than when diphtheria toxoid is administered alone (group 9).

Accordingly, for the reasons given above, applicants respectfully request that the rejection of claims 1-3 and 13-20 under 35 U.S.C. 103(a) over Schmitt et al., Alpar et al. and Isaka et al. be reconsidered and withdrawn.

In view of the above, allowance of the pending claims is earnestly requested. If the examiner has any questions regarding this amendment, she is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,



Edna I. Gergel, Ph.D.
Registration No. 50,819
Agent for Applicants

HOFFMANN & BARON, LLP
6900 Jericho Turnpike
Syosset, New York 11791
Tel. 516-822-3550
Fax. 516-822-3582

233811_1